Signet ring lymphoma: a potential diagnostic mishap

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Signet ring lymphomas are proliferations of malignant lymphoid cells containing cytoplasmic inclusions or vacuoles that displace the nucleus to the side, imparting a "signet ring" appearance. These signet ring cells, particularly those with cytoplasmic vacuoles, may be mistaken for an adenocarcinoma rather than a lymphoma, if sufficient material is not available to differentiate the case by immunohistochemical stains or flow cytometry. The pathologist must also be aware of this entity so that appropriate studies may be untaken.

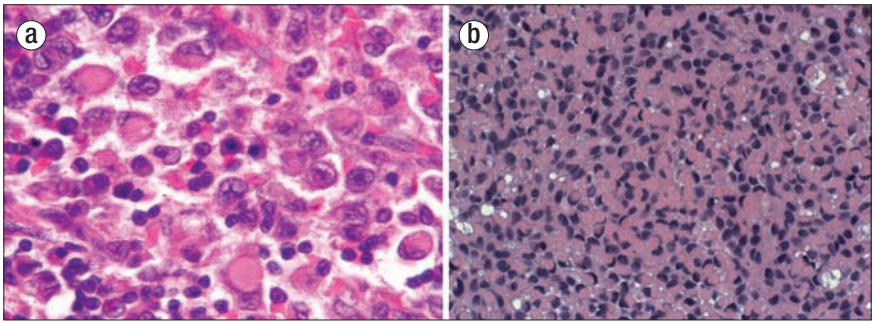

Figure 1. (a) Biopsy of inguinal lymph node. Lymphoma with signet rings with eosinophilic inclusions. Hematoxylin and eosin (H&E) ×500. **(b)** Adenocarcinoma of stomach. Signet rings with eosinophilic inclusions. H&E ×200.

Signet ring lymphomas are proliferations of malignant lymphoid cells with cytoplasmic inclusions or vacuoles that displace the nucleus to the side of the cell, imparting a "signet ring" appearance. The cytoplasm may appear eosinophilic or clear and thus may mimic the appearance of adenocarcinoma cells. With the increasing use of cytology aspiration specimens or fine needle core biopsies, the presence of these vacuolated cells may be mistaken for an adenocarcinoma rather than a lymphoma if sufficient material is not available to further differentiate these specimens by immunohistochemical stains and perhaps flow cytometry. The pathologist must also be aware of this entity so as to obtain or order additional diagnostic studies. Examples are given to illustrate cases of signet ring lymphoma with comparison to adenocarcinoma.

CASE 1

A 62-year-old man who had a history of prostatic carcinoma developed inguinal lymphadenopathy. A needle core biopsy was performed on an inguinal node. The microscopic slides revealed cells with eccentric nuclei and eosinophilic cytoplasm *(Figure 1a)*. A CD45 (leukocyte common antigen) stain was positive, indicating a hematopoietic neoplasm rather than a carcinoma. Sufficient material was available to do additional stains, and a CD20 stain (a B cell marker) and CD10 stain (a germinal center marker) were positive, favoring a B-cell lymphoma of possible follicular origin. Contrast Figure 1a with an adenocarcinoma of the stomach with eosinophilic cytoplasm *(Figure 1b)*.

CASE 2

A 41-year-old woman had a history of a gastric carcinoma 2 years earlier. The patient developed abdominal pain, and a peripancreatic mass was discovered by a computed tomography (CT) scan. A CT ultrasound–guided fine needle aspiration yielded tissue composed of "signet ring" cells *(Figure 2a)*. The initial impression was recurrent adenocarcinoma. However, cytokeratin and mucicarmine stains were negative on the cell block, which would be expected to be positive in adenocarcinoma. Since the cell block specimen was limited, CD45, CD20, and CD3 (T-cell marker) immunohistochemical stains were done, and CD45 and CD20 were positive, indicating a B-cell lymphoproliferative process. No further tissue was obtained, and the patient was placed on a regimen including rituximab (Rituxan), which resulted in a regression of the peripancreatic mass. Contrast Figure 2a with a pancreatic adenocarcinoma *(Figure 2b)*.

CASE 3

A 36-year-old man was found to have a large mesenteric mass. An ultrasound-guided fine needle aspirate yielded only a small sample containing atypical signet ring cells, which were

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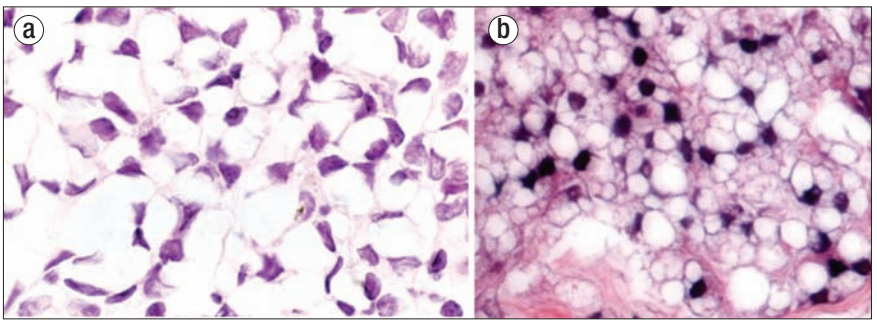

Figure 2. (a) Peripancreatic biopsy. Lymphoma with signet rings and clear cytoplasm. H&E ×400. **(b)** Adenocarcinoma of the pancreas. Signet rings with clear cytoplasm. H&E ×400.

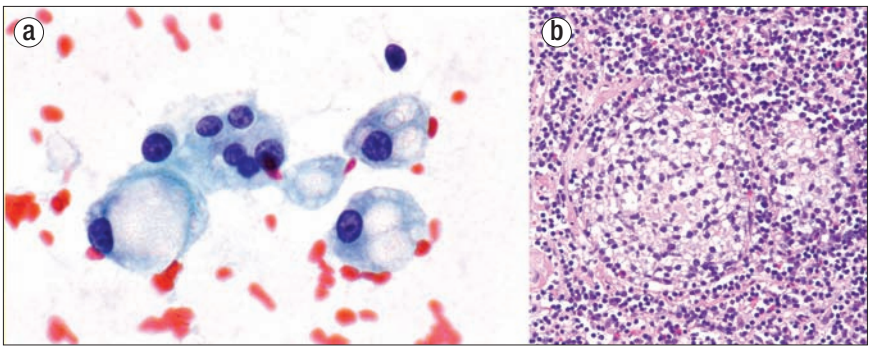

Figure 3. (a) Aspiration biopsy of abdominal mass. Signet rings. H&E ×400, Papanicolaou stain ×400. **(b)** Follicular lymphoma composed of signet ring cells. H&E ×200.

not diagnostic but suspicious for malignancy. An open excisional biopsy was then done, which revealed a signet ring variant of a follicular lymphoma *(Figure 3)*.

DISCUSSION

The first cases of signet-ring lymphoma were reported by Kim et al in 1978 (1). They described seven cases of non-Hodgkin's lymphoma characterized by an abundance of cells containing clear vacuolated cytoplasm. Since this original description by Kim, approximately 50 cases of signet ring lymphoma have been reported in the literature. The majority of cases involved lymph nodes, and bone marrow involvement appears to be uncommon. The majority of cases have been of B-cell lineage, and most have been associated with follicular lymphoma (1–3) with less association with other B-cell lymphoproliferative disorders (4–9). A few cases of signet ring T-cell lymphoma and anaplastic large-cell lymphoma have also been reported (10–12).

Signet ring lymphomas with clear cytoplasm typically express immunoglobulin (Ig) with a predominance of lambda light chains, while those cases with eosinophilic globules in the cytoplasm are periodic-acid-Schiff positive and more commonly express IgM (1, 3). Clinically follicular lymphomas with the signet ring morphology do not differ in behavior from the more typical follicular lymphoma, and prognosis depends more on grade (1 and 2 low grade and 3A and 3B high grade).

The importance of signet ring lymphoma is not to mistake it for adenocarcinoma, particularly when sample size is limited. It is important that sufficient material is present to perform the necessary immunostains and flow cytometry to differentiate lymphoma from carcinoma. Whenever possible, open biopsies should be performed if the lymph node is readily accessible. At times the location of the tumor and status of the patient will dictate that a fine needle aspiration or core biopsy be obtained. This latter situation is more likely to cause a diagnostic problem. The pathologist also needs to be aware of lymphomas containing signet ring cells so as to obtain the necessary diagnostic stains to make the correct diagnosis.

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